(i) transforming a [eucaryotic] eukaryotic cell with a first DNA [sequence] construct encoding a first indicator component under the control of a promoter having restricted expression;

(ii) transforming the cell of (i) or a descendent of the cell by operably integrating into the cell's genome, a second DNA construct comprising DNA [lacking a promoter but which comprises a sequence] encoding a second indicator component not operably linked to a transcription control element;

(iii) producing tissue or specialized cells from the cell of (ii); and

(iv) monitoring the tissue or specialized cells of (iii) for a detectable indicator resulting from both the first and second indicator components indicative of integration of the second DNA construct into a gene having restricted expression.

6. (Amended) The method of [any one of claims 1-5] claim 1 which additionally comprises [the additional step of] isolating DNA endogenous to the eucaryotic cell which flanks [integrated DNA comprising the second indicator component] the second DNA construct integrated into a gene having restricted expression.

9. (Amended) A DNA construct comprising, in a 5' to 3' direction, a splice acceptor, [and] a sequence encoding an ~~inactive~~ subunit or fragment of an enzyme and, an IRES ~~wherein said~~ sequence encoding is not operably linked to a transcription control element, and wherein said subunit or fragment is active when combined with a further subunit or fragment of an enzyme.

12. (Amended) The combination of:

(i) a DNA construct for integration into the genome of an [eucaryotic] eukaryotic cell comprising a sequence encoding a first indicator component under the control of a promoter having restricted expression; and

(ii) a DNA construct for integration into the genome of a [eucaryotic] eukaryotic cell, comprising in the 5' to 3' direction, a splice acceptor, [and] a sequence encoding a second indicator component not operably linked to a transcription control

B4

element and an optional IRES, wherein expression of both the first and second indicator components in said cell is detectable.

Please add the following new claims:

Sub C3

--15. A DNA construct comprising, in a 5' to 3' direction, a splice acceptor and a sequence encoding an inactive alpha or omega fragment of β-galactosidase, wherein said sequence encoding is not operably linked to a transcription control element and said fragment is active when combined with another fragment of β-galactosidase.

Sub F2

16. The method of claim 1, wherein:

(i) in the first DNA construct, DNA encoding the first indicator component is separated from the promoter having restricted expression by a sequence of DNA which prevents transcriptional control by said promoter over the DNA encoding the first indicator component;

B5

(ii) in the second DNA construct, the second indicator component is a recombinase capable of removing the sequence of DNA preventing transcriptional control in the first DNA construct; and,

wherein said monitoring is for cells in which the first indicator component is expressed under the transcriptional control of the promoter having restricted expression.

11 ~~17.~~ 15 The method of claim ~~16~~ wherein the DNA preventing transcriptional control is flanked by lox sites and the recombinase is Cre.

Sub D4

18. A method of producing eukaryotic tissue or specialized cells comprising a detectable indicator associated with a target gene having restricted expression, which comprises:

(i) transforming a eukaryotic cell with a first DNA construct encoding a first indicator component under the control of a promoter having restricted expression;

(ii) transforming the cell of (i) or a descendent of the cell by integrating into the cell's genome, a second DNA construct comprising DNA encoding a second indicator component not operably linked to a transcription control element;

(iii) producing tissue or specialized cells from the cell of (ii); and

(iv) selecting tissue or specialized cells of (iii) by the presence of a detectable indicator resulting from both the first and second indicator components.

19. A method of producing a mouse or a pig comprising a detectable indicator associated with a target gene having restricted expression, which comprises:

(i) transforming a murine or porcine ES cell with a first DNA construct encoding a first indicator component under the control of a promoter having restricted expression;

(ii) transforming the cell of (i) or a descendent of the cell by integrating into the cell's genome, a second DNA construct comprising DNA encoding a second indicator component not operably linked to a transcription control element;

(iii) selecting transformed cells of (ii);

(iv) introducing selected cells of (iii) into a murine or porcine host embryo;

(v) implanting the host embryo of (iv) into a pseudopregnant mammal;

(vi) maintaining the mammal of (v) while offspring develops to term from the host embryo; and

(vii) selecting offspring of (vi) by the presence of a detectable indicator resulting from both the first and second indicator components in tissue or specialized cells of the offspring.--

REMARKS

In the Office Action, claims 7-14 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled. Claims 1-8 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claim 9 was rejected under 35 U.S.C. § 102(b) as allegedly